Remarks

Claims 1, 7, 12, 14 and 17 have been amended. Claim 19 has been cancelled without prejudice or disclaimer and with the understanding that Applicants may pursue the subject matter encompassed by the cancelled claim in a continuation application.

The amendment to claims 1, 7, 12, 14 and 17 that adds the feature regarding the difference in the rate of precipitation of the dissolved Agent in the presence of a water-soluble cellulose ether or an ester of a water-soluble cellulose ether after the pH of the medium in which the Agent is present is shifted from 1.5 to 6.5 as compared to the rate of precipitation of the Agent alone under the same conditions, finds full support in Applicants' published specification at, *inter alia*, paragraphs [0008], [0013] and [0171] to [0177].

The amendment to claims 1, 7, 12, 14 and 17 that indicates that the recited amount of the Agent will be at least 90% dissolved under the recited acid conditions finds full support in Applicants' specification at, *inter alia*, Table 2 (Example 9 entry).

The other amendments to the claims are simply formalistic in nature. Accordingly, no new matter has been added by any of the amendments.

1. **Rejections under 35 U.S.C. § 112, second paragraph**

A. "substantially completely dissolve"

Claims 1-19 are rejected as being indefinite because the Examiner asserts that the metes and bounds of the recitation "will substantially completely dissolve" are not clear and concise.

Without acquiescing to the Examiner's rejection, Applicants have, in order to expedite prosecution, replaced this phrase with "will be at least 90% dissolved" which finds full support in Applicants' specification as addressed in the Remarks section above. In view of this amendment to claims 1, 7, 12, 14 and 17, Applicants respectfully request that this rejection be withdrawn.

B. "the Agent"

Claims 1-19 are rejected as being indefinite because the Examiner asserts that parenthetical information can be interpreted as a claim limitation.

Applicants believe that the use of the phrase "the Agent" as a shorthand reference for the chemical compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline or a pharmaceutically acceptable salt thereof is entirely proper and should not render indefinite any claims in which it appears. However, in an effort to expedite prosecution of the subject application, Applicants have further amended the phrase "the Agent" to "hereinafter, the Agent" to remove any perceived indefiniteness by the Examiner. In view of this amendment, Applicants request that this rejection be withdrawn.

C. Claim 19

Claim 19 is rejected as allegedly incomplete for omitting essential steps where the claimed method reduces inter-patient variability.

Without acquiescing to the Examiner's rejection, Applicants have cancelled claim 19 without prejudice or disclaimer.

2. <u>Rejection under 35 U.S.C. 103(a)</u>

Claims 1-19 are rejected as unpatentable over U.S. Patent No. 5,770,599 to Gibson ("Gibson") in view of U.S. Patent No. 6,410,054 to Thosar *et al.* ("Thosar"). The Examiner asserts that Gibson teaches that 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline can be formulated into pharmaceutical compositions comprising conventional excipients. The Examiner further asserts that Thosar teaches immediate release formulations of the compound eplerenone that include, for example, hydroxypropyl methylcellulose as a coating material. According to the Examiner, absent a demonstration of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicants' invention to prepare a composition containing 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline and water-soluble cellulose ethers.

Applicants have amended claims 1, 7, 12, 14 and 17 to recite that the water-soluble cellulose ether or ester of a water-soluble cellulose ether is present in a pharmaceutical composition of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline

or a pharmaceutically acceptable salt thereof ("the Agent") in an amount effective to slow the rate of precipitation of the dissolved form of the Agent after the pH of the medium in which the Agent is present is shifted from 1.5 to 6.5 as compared to the rate of precipitation of the Agent alone under the same conditions. Applicants observed that while the Agent had a high solubility in an acidic medium similar to the stomach, the Agent was prone to precipitate from solution as the pH of the medium shifted to a higher (*i.e.*, more alkaline) pH similar to that of the upper GI tract (see, *e.g.*, paragraph [0008] of Applicants' specification). Such observed sensitivity of the Agent to changes in pH can be attributed to the presence of basic nitrogen atoms in the Agent's structure (see *e.g.*, paragraph [0005] of Applicants' published application). It was surprisingly discovered by Applicants that the rate at which the Agent precipitated from solution as the pH increased was significantly reduced when the Agent was in the presence of water-soluble cellulose ethers or esters of water-soluble cellulose ethers such as, for example, hydroxypropyl methylcellulose.

Neither Gibson nor Thosar teach or suggest this unexpected result discovered by Applicants. The Examiner relies on Gibson for the general teaching that the Agent may be "prepared in a conventional manner using conventional excipients." Thosar is relied upon for teaching immediate release formulations that contain hydroxypropyl methylcellulose as a exemplary water-soluble cellulose ether. Applicants submit that Thosar is limited to formulations of the specific compound eplerenone, the structure of which is depicted in Thosar as Formula I at the bottom of column 1. An analysis of the structure of eplerenone reveals that it is essentially pH independent because it does not contain acidic or basic functionalities capable of forming salts, such as, for example, basic nitrogen atoms. Support for this characterization of eplerenone may be found, for example, in the disclosure of a NDA document for eplerenone tablets, the first page of which is submitted herewith for the Examiner's consideration. Accordingly, a person of ordinary skill in the art would not be motivated to combine a water-soluble cellulose ether (such as the hydroxypropyl methylcellulose described in Thosar) with the Agent for the purpose of addressing a potential precipitation problem that is pH dependent.

More specifically, hydroxypropyl methylcellulose is described in Thosar as "a preferred binding agent used [to] impart cohesive properties to the powder blend of the eplerenone

formulation" (col. 9, lines 56-58) or as a coating material for use in controlled release compositions (see col. 20, lines 19-26). Neither of these teachings contemplates the use of hydroxypropyl methylcellulose, or more broadly, water-soluble cellulose ethers, as a means for retarding the precipitation of the pH-sensitive Agent as the pH of the environment in which the Agent is present increases. A person of ordinary skill in the art, based on a reading of Thosar, would therefore not have a reasonable expectation of success in using hydroxypropyl methyl cellulose for this purpose and accordingly would not be motivated to combine hydroxypropyl methylcellulose with a compound such as the Agent.

In summary, Applicants have discovered that the rate of precipitation of a pH-sensitive compound (*i.e.*, the Agent) that is highly soluble in acidic aqueous media and less soluble at increased pH is unexpectedly slowed following a shift in the pH of the media to 6.5 when the compound is in the presence of a water-soluble cellulose ether or ester thereof. In contrast, Thosar is directed toward methods of solubilizing a largely water-insoluble, pH-insensitive compound (*i.e.*, eplerenone) in aqueous media to increase the bioavailability of the compound. Nothing in Thosar teaches or suggests that the presence of hydroxypropyl methylcellulose has the effect of reducing the rate of precipitation of solubilized eplerenone following a shift to a higher pH. Gibson cannot remedy these deficiencies present in Thosar. Accordingly, a person of ordinary skill in the art would not have a reasonable expectation of success in combining the teachings of Thosar with Gibson to arrive at Applicants' claimed composition.

For at least these reasons, Gibson, either alone or in combination with Thosar, cannot render Applicants' claimed subject matter obvious. Applicants therefore request that this rejection be withdrawn.

3. Conclusion

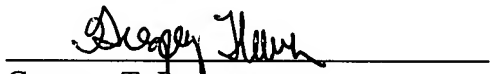
The foregoing amendments and remarks are being made to place the application in a condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which my be required, including any required extension of time fees, or
to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: May 29, 2007

Respectfully submitted
Morgan, Lewis & Bockius LLP

Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: 202-739-3000
Fax: 202-739-3001



Gregory T. Lowen
Registration No. 46,882
Direct: 202-739-5915

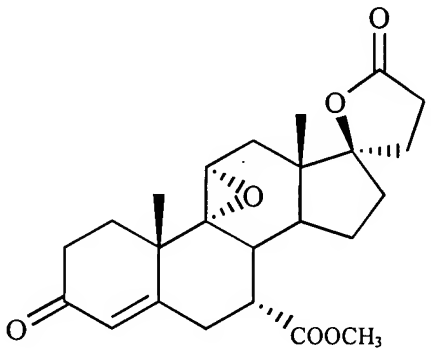
INSPRA™

eplerenone tablets

DESCRIPTION

INSPRA™ contains eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor.

Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α,11α,17α)-. Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. The structural formula of eplerenone is represented below:



eplerenone

Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

INSPRA for oral administration contains 25 mg or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol,